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EXAMINER
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This is a communication from the examiner in charge of your application
COMMISSIONER OF PATENTS AND TRADEMARKS

18 October 1993
☒ This application has been examined ☒ Responsive to communication filed on 3 Nov. 1993 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire three (3) month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 25, 26, 28, 42-46 and 48 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☒ Claims 1-24, 29-41, and 56-59 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 25, 26, 28, 42-46, and 48 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

The text of those sections of Title 35, U. S. Code not included in this action can be found in a prior Office Action.

The Office notes that the preliminary amendment filed 3 November 1993 cancels non-elected claims 1-24, 29-41, and 56-59. The amendment to the pending claims in the previously unentered amendment under 37 CFR 1.116 bearing a mail room date of 18 October 1993 has been entered. Thus, claims 25, 26, 28, 42-46, and 48 are amended and claims 27, 47, and 49-55 have been canceled. The pending claims are 25, 26, 28, 42-46, and 48.

The specification at page 1 should contain as the first paragraph, the continuing status of the present application with respect to the parent application. Note that item 6 of the request for filing a continuation indicates no status to be accorded to the present application with respect to any parent application.

In view of pending claims are 25, 26, 28, 42-46, and 48 the following grounds of objection and rejection are or remain applicable to the pending claims.

The specification remains objected to under 35 U.S.C. 112, first paragraph, as failing to provide a reasonable written description, enablement and best mode for practicing the claimed invention because the specification does not disclose how the initial FRT site is precisely inserted (i.e., targeted) to the specific DNA. Note that precise genomic targeting requires not only the DNA to be inserted but that the location to which it is to be inserted also be precisely identified. Absent such teaching, it cannot be said that the DNA to be targeted to the first preexisting site is precisely targeted to some known location on a DNA when that location on the DNA is unspecified. Since the integrating DNA recombines with the FRT site, but where the location of the preexisting site is unspecified, there is no precisely targeting the integrating DNA to any specified location in the genome; i.e., the problem of inability to control the location of integration of the initial FRT site remains as the specification does not disclose how the initial FRT is integrated at predetermined sites on a chromosome. See present specification page 12, paragraph bridging pages 12-13. How does the first FLP site get specifically and precisely integrated into the genome? Note that the first full paragraph of present specification page 12 dose not detail how this is done and is subject to the inability to control the site of integration referred to at present specification page 1.

Claims 25, 26, 28, 42-46, and 48 are rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth in the objection to the specification...

Claims 25, 26, 28, 42-46, and 48 are rejected under 35 U.S.C. 112, first paragraph, as the disclosure is not enabled for precisely targeting the second DNA when the site of that integration (i.e., the first FLP recombination target site) is not precisely predetermined by its own location in the genome of the cell. From the present specification, there is no disclosure of how this is accomplished. How does the first FLP site become specifically and precisely integrated into the genome? Note that the first full paragraph of present specification page 12 does not detail how this is done and is subject the inability to control the site of integration referred to at present specification page 1. Here, where the specification does not disclose how this is done, it would have required undue experimentation on the part of one skilled in the art to have used the present application disclosure to precisely place the first FLP target recombination site at a prespecified location and where there are no other indvertent sites where the first FLP recombination target site becomes integrated into the genome. Note that the present claims call for the first FLP target recombination site to be precisely placed else the precise location of the integrating DNA is not definable. See MPEP 706.03(n) and 706.03(z).

Insofar as the response filed 18 October 1993 comments upon objections to the specification and rejection of claims under 35 U.S.C. 112 first paragraph, the comments in the response are not convincing for the above indicated reasons.

Claims 25, 26, 28, 42-46, and 48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 25 is indefinite as it is unclear whether the item (i) "... first FLP recombination target site (FRT) ..." which contains an FRT is or is not that recited in item (ii) as the "... a first DNA comprising a nucleotide sequence containing at least one FRT ...". Moreover, in claims 25 and 26, the recitation of "in the presence of an FLP recombinase" is indefinite in the claimed process as no biological action is recited as effected by the recombinase (which is not even indicated as inside the cells). Note that the excising is not indicated as a brought about by the action of the recombinase as contacting does not indicate the action effected by the recombinase. In the pending claims it is also unclear as to whether or not the cells contain any naturally occurring FRT sites the unknown location of

which would affect the recited "precise targeting". Claims 43 and 44 are indefinite as to the recitation of "within a functional portion ...". What is the function of the portion recited in the claims? What defines "a functional portion"? What functional portions are referred to in the claims and how big is a functional portion in nucleotide bases (is it one base or $5X10^6$ bases)?

Claims 25 and 28 are rejected under 35 U.S.C. 102 (b) as anticipated by or, in the alternative, under 35 U.S.C. 103 as obvious over Golic *et al.* which discloses site specific recombination in *D. melanogaster* using DNA coding for FLP and FRT (see at least pages 499 and 507) where it is indicated that FRT bearing plasmids can be directed to the site of an FRT already resident in the genome for germline transformation which would have resulted in a process for producing the host organism. The step of mating the flies (page 500), is a step of introducing into the cells (which are indicated as already having an FRT site (page 499) in the *w* gene) that are the male or female gametes into the other *D. melanogaster* gamete wherein Golic *et al.* disclose that FLP catalyzed recombination between FRTs in the germline and the soma. In the alternative, it would have been obvious from the disclosure which indicates that "we expect the it will work in other organisms as well" to expect the process to function in other organisms which are higher eukaryotes (page 499, left column) where mammalian cells (page 499 right column) are known higher eukaryotic cells.

The comments (page 12) in the response filed 18 October 1993 as to this ground of rejection are noted but are not convincing for the above stated reasons.

Claims 25, 26, 28, 42-46, and 48 remain rejected under 35 U.S.C. 103 as being unpatentable over Sauer (U.S. '317) taken with Golic *et al.* as indicated in the prior Office Actions of the parent application as restated below.

Sauer teaches site specific recombination of mammalian cells (col 14+) using plasmids with the DNA coding for the *cre* and *lox* (cols 1, 6-7). Where Sauer does not explicitly disclose the use of DNA coding for FLP and FRT, it would have been obvious to one of ordinary skill in the art to use DNA coding for FLP and FRT in vectors for transforming *D. melanogaster* because Golic *et al.* discloses site specific recombination in *D. melanogaster* with DNA coding for FLP and FRT (see at least pages 499 and 507) where it is indicated that FRT bearing plasmids can be directed to the site of an FRT already resident in the genome

suggesting its use for germline transformation which would have resulted in a transgenic animal and further indicate that "we expect the it will work in other organisms as well" which would have motivated one of ordinary skill in the art to combine the teachings of Sauer which discloses at cols 14+, site specific recombination in mammalian cells (mouse) where the combination of the Sauer and Golic *et al.* references would have resulted in a method for site specific recombination in mammalian cells or in transgenic animals. Moreover, where both Sauer and Golic *et al.* teach that the DNA for the FLP and FRT are from yeast, Sauer teaches at col 5, mating the yeast of opposite mating types which contain the plasmids with the DNA for the FLP and FRT which is a step of introducing the cells produced by the step (i) and (ii) of claim 28 into the subject where the subject is another yeast cell and where Golic *et al.* disclose mating the flies (page 500), it is a step of introducing the cells which are the male or female gametes into the subject where the subject is the other *D. melanogaster* gamete which after fertilization becomes a transgenic fruit fly. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was a whole, clearly prima facie obvious.

Claims 25, 26 and 28 are rejected under 35 U.S.C. 103 as being unpatentable over Sauer (U.S. '317) taken with Golic et al. as applied to claims 25, 26, 28, 42-46, and 48 above, and further in view of Palmiter *et al.* as directed to the "mammalian host cell" as being in a transgenic animal for the reasons indicated in the Office Actions of the parent application as restated below.

Sauer and Golic *et al.* are applied as indicated above and where Golic *et al.* indicates expectation of success as indicated above, one of ordinary skill in the art would have found it obvious to combine the teachings in the Palmiter *et al.* reference which discloses introduction of the transforming DNA into totipotent teratocarcinoma cells or embryonic stem cells which can be introduced into the developing embryo by aggregation of the cells. Here, where Sauer taken with Golic *et al.* disclose the plasmids with the FLP and FRT DNA for site specific recombination, it would have been obvious to one of ordinary skill in the art given that Golic *et al.* indicate that "we expect that it will work in other organisms as well", to modify the process by using totipotent teratocarcinoma cells or embryonic stem cells as disclosed by Palmiter *et al.* which are later aggregated with the developing mouse embryo. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was a whole, clearly *prima facie* obvious.

The comments (pages 12-18) of the response filed 18 October 1993 have been considered but are not persuasive as to applicant's stated disagreement in the paragraph spanning pages 12-13 as the reasons for combining the cited references have been put forth in the stated grounds of rejection under 35 U.S.C. 103.

As to the discussion of gain and loss of function, such discussion is also found in at least Golic *et al.* - see the abstract and the relevant pages discussing the gain and loss of function as to the eye color as well as for example at col 7 of Sauer.

As to the discussion of the Sauer reference, at page 14, it is noted that the response discusses P1, *Cre* and *lox*, however, the comments are unconvincing as Golic *et al.* discloses site specific recombination in *D. melanogaster* with DNA coding for FLP and FRT (see at least pages 499 and 507) where it is indicated that FRT bearing plasmids can be directed to the site of an FRT already resident in the genome suggesting its use for germline transformation which would have resulted in a transgenic animal and further indicate that "we expect the it will work in other organisms as well" which would have motivated one of ordinary skill in the art to use other cells such as those cells and teeachings in the Sauer patent which discloses at cols 14+, site specific recombination in mammalian cells (mouse) where the combination of the Sauer and Golic *et al.* references would have resulted in a method for site specific recombination.

The paragraph bridging pages 14-5 of the response discusses the Golic *et al.* reference but is unconvincing because the P-element was used to introduce the FRT, not to effect its function wherein the Golic *et al.* and the Sauer references discuss gain of function via recombination events such as gene duplication (and recombination inversion of the coding sequence, see at least col 7 of Sauer) and that the yeast system FLP/FRT effects site specific recombination in a eukaryotic cell.

As to the discussion at page 15 of applicant's response, the discussion of the "gain of function system" the comments are not commensurate to the recitation in the present claims - there is no discussion of ß-galactosidase. The discussion of precise reorganization of the DNA is noted but not convincing as the location of the first (preexisting) FRT recited in the present claims and present specifiation is not established. From the cited references, it is clear that the site of recombination is where the FRT is located. This is the same as in the present application. Thus, the comments are not persuasive.

At page 16, the response asserts that there is no teaching or suggestion of accurate and routine reproduction of functional translational reading frames. This is not convincing. Note that the Golic *et al.* reference discloses gene duplication effected by the recombinase which duplication also effected return of red eye color as a function of expression of a protein (i.e., a functional translational reading frame) and wherein Sauer discloses (see at least column 7), a precise recombination event that effects reconstruction of a functional transcriptional and translational reading frame where the analogous FLP/FRT constructs would have been expected to effect a reconstruction of a functional transcriptional and translational reading frame. Thus, the comments in applicant's response is not convincing.

The comments (paragraph bridging pages 16-17) in the response argue that the parameters disclosed by Golic *et al.* are specific to *Drosophila* such comments are unconvincing as the rejection is based upon the combined references of Golic *et al.* and Sauer wherein Golic *et al.* contrary to applicant's assertion is not limited to *Drosophila* as the Golic *et al.* reference indicates that the process use of yeast FLP/FRT site specific recombination is expected to work in other organisms (mammalian cells, page 499) where Sauer disclose that using an analogous system to the FLP/FRT of yeast, site specific recombination was obtained where application of the teachings in the Golic *et al.* reference to the yeast FLP/FRT modified by the disclosure of the Sauer patent teachings such as using mammalian cells and engineered genes would have resulted in the claimed processes.

In the first full paragraph of page 17, applicant's response asserts a lack of motivation to combine because of an asserted lack of efficiency. This is not convincing in view of the stated grounds of rejection above. Note that even where applicant's response asserts lack of efficiency, the combined cited references disclose collectively to one of ordinary skill in the art that the yeast FLP/FRT works and is expected to work in other systems/organisms wherein Sauer discloses an that one such system using analogous constructs to the yeast FLP/FRT functions in the manner of the present claims.

As to the discussion of the Palmiter *et al.* reference, the response asserts that it does not cure any deficiencies, however, given the above indicated grounds of rejection and the unconvincing reasons in the response filed 18 October 1993, the statement in the response as to the Palmiter *et al.* reference is not convincing.

It is noted that the response (last full paragraph of page 17) cites *In re Gordon* regarding hindsight analysis. This is not well taken as none was used, needed, employed, argued, asserted, suggested, inferred, implied, or in any other way necessary or applied. The references are properly combined by at least the disclosure and suggestion in the Golic *et al.* reference to apply use of the yeast FLP/FRT system to other systems/organisms where Sauer discloses analogous constructs and processes where application of the teachings in the combined references would have resulted in processes using the yeast FLP/FRT to accomplish the processes disclosed in Golic *et al.* as well as those disclosed by Sauer. In view of the foregoing, the comment in the response as to hindsight is not convincing as citation of pertinent art as is properly combined, is not hindsight. See *In re Winslow*, 151 USPQ 48 (CCPA 1966), which indicated that the claims are rejected when by merely applying the prior art knowledge one of ordinary skill in the art arrives at the claimed invention. The one of ordinary skill in the art is presumed to have full knowledge of the prior art in the field of endeavor and it is pointed out that application of the prior art is not to be misconstrued as hindsight but merely selection and application by the Examiner of pertinent art as is required; and, as pointed out more recently (*In re Nilssen*, 7 USPQ2d 1500 (CAFC 1988)), that hypothetical person of ordinary skill in the art is assumed to have knowledge of all prior art in the field of the inventor's endeavor, of prior art solutions for a common problem as is the case here even if outside the field, and that for the purposes of combining references which here are combined by suggestion founded in the prior art as indicated in the grounds of rejection, those references need not explicitly suggest combining teachings. Thus, the commentary in the response as to hindsight as unlike the issue in the *In re Gordon* decision, there is no apparatus, there is no need to turn anything upside down, but there is a clear suggestion to one of ordinary skill in the art that the constructs are expected to work where substitution of the yeast FLP/FRT for the analogous constructs would have been expected to work and here, even where the substitution of the yeast FLP/FRT is made, the original intended purpose of the invention disclosed and claimed in the Sauer patent does not become inoperable, rather it is enhanced because the yeast FLP/FRTs provide constructs that effect the same processes disclosed and claimed in the patent. Thus, the citation of *In re Gordon* does not support the assertions made in the response.

in is unconvincing as are the comments at page 18 of the response as to applicant's conclusion.

No claim is allowed.

Papers related to this application may be submitted by facsimile transmission to Group 1800 via the PTO Fax Center located in Crystal Mall 1 (CM1) and must conform to the notice published in the Official Gazette, 1096 OG 30 (15 November 1989). The telephone numbers for the CM1 PTO Fax Center are (703) 308-4227 and 305-3014.

An inquiry concerning this communication should be directed to Christopher Low at telephone number (703) 308-0196.

Christopher S.F. Low

CSFL
03 February 1994

CHRISTOPHER S. F. LOW
PRIMARY EXAMINER
GROUP 1800